

# PATENT SPECIFICATION

(11) 1265 615

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## NO DRAWINGS

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(51) International Classification C 07 c 103/40

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C2C 20Y 220 227 22Y 292 29X 29Y 30Y 313 31Y 320  
321 32Y 332 339 342 34Y 360 362 366 367 368  
36Y 591 62X 658 65X 747 790 KN LA

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A2E 4

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## (54) SPRAY DRYING PROCESS

### ERRATA

SPECIFICATION No. 1,265,615

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Page 1, line 11, for water-soluble read water-soluble

Page 1, line 68, for sub- read sub-

Page 2, line 7, for maintain read maintained

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Page 3, line 47, for this read thus

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ensures an optimum careful treatment of the material to be dried and thus is especially suitable for pharmaceuticals which are sensitive to hydrolysis but freeze-drying plants have the disadvantage of being very expensive not only in the provision thereof but also in operation; furthermore, the capacity of such plants is relatively low, due to the necessarily discontinuous method of operation and the comparatively high cost of apparatus.

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Consequently, attempts have been made to replace freeze drying by the cheaper and simpler process of spray drying at low temperatures however, these attempts have been unsuccessful because the droplets which are formed in the spraying of very viscous or hygroscopic liquids merely inflate to form hollow spheroids with residual water in the middle which subsequently agglomerate to form lumps which can subsequently only be dissolved again with great difficulty. This undesirable effect can admittedly be countered by a drastic increase of the drying temperature but this leads to damaging of the

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reference are immediately formed due to the evaporation of the solvent but, before the formation of a dry and thus sufficiently stable skin, they explode and those again collapse. The small amount of solvent (2-6%) has, in the meantime, evaporated so that, in the same way as in the case of spray drying without the addition of solvent, lumps are formed which considerably impair not only the further drying but also the redissolving of the dry substance. It should also be mentioned that the dried materials also sub-  
bornly retain not inconsiderable amounts of the solvent so that they cannot be used as pharmaceuticals for parenteral administration.

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We have now found that the above-mentioned disadvantages can be avoided in a simple manner by the addition of ammonium salts of volatile acids to the aqueous solutions of the substance to be dried.

As ammonium salts of volatile acids, ammonium bicarbonate is preferred but there can also be used, for example, ammonium nitrite.

Not only the bulk volume but also the residual moisture in the dried product is

SEE ERRATA SLIP ATTACHED

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(72) Inventors PETER RIECKMANN  
GREGOR GROPPENBACHER  
WERNER ROTHE and JURGEN SCHELLHORN



## (54) SPRAY DRYING PROCESS

(71) We, BOEHRINGER MANNHEIM G.M.B.H., of Mannheim-Waldof, Germany, a Body Corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with a spray drying process for the preparation of readily water-soluble friable dry powders and granulates.

For recovering labile dry substances from solutions, there can only be used drying processes which operate at low temperatures. The so-called freeze drying process admittedly ensures an optimum careful treatment of the material to be dried and thus is especially suitable for pharmaceuticals which are sensitive to hydrolysis but freeze-drying plants have the disadvantage of being very expensive not only in the provision thereof but also in operation; furthermore, the capacity of such plants is relatively low, due to the necessarily discontinuous method of operation and the comparatively high cost of apparatus.

Consequently, attempts have been made to replace freeze drying by the cheaper and simpler process of spray drying at low temperatures; however, these attempts have been unsuccessful because the droplets which are formed in the spraying of very viscous or hygroscopic liquids merely inflate to form hollow spheroids with residual water in the middle which subsequently agglomerate to form lumps which can subsequently only be dissolved again with great difficulty. This undesirable effect can admittedly be countered by a drastic increase of the drying temperature but this leads to damaging of the

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material to be dried, even in the case of very short drying time.

In order to overcome this problem, it was suggested some years ago to add to the aqueous solutions or suspensions, before the spray drying, a low boiling solvent which was intended to explode the above-mentioned hollow spheroids during the drying process due to its high vapour pressure (see Chemiker-Zeitung, 15/16, 156/1942).

In experiments which we have carried out, we have now found that the desired effect is not obtained in the case of the drying of hygroscopic and/or viscous liquids. The hollow spheroids mentioned in the above literature reference are admittedly formed due to the evaporation of the solvent but, before the formation of a dry and thus sufficiently stable skin, they explode and those again collapse. The small amount of solvent (2—6%) has, in the meantime, evaporated so that, in the same way as in the case of spray drying without the addition of solvent, lumps are formed which considerably impair not only the further drying but also the redissolving of the dry substance. It should also be mentioned that the dried materials also sub-  
stantially retain not inconsiderable amounts of the solvent so that they cannot be used as pharmaceuticals for parenteral administration.

We have now found that the above-mentioned disadvantages can be avoided in a simple manner by the addition of ammonium salts of volatile acids to the aqueous solutions of the substance to be dried.

As ammonium salts of volatile acids, ammonium bicarbonate is preferred but there can also be used, for example, ammonium nitrite.

Not only the bulk volume but also the residual moisture in the dried product is

SEE ERRATA SLIP ATTACHED

dependent upon the concentration of the ammonium salts in the wet material. Since these properties are also dependent, to a large extent, upon the product the optimum concentration should be previously ascertained by experimental dryings. However, the concentration is maintain approximately within the limits of 2—5%; in the case of ammonium bicarbonate, it is about 3%.

Thus, according to the present invention, there is provided a spray drying process for the preparation of readily water-soluble, friable dry powders or granulates, wherein to an aqueous solution of a substance to be dried, before carrying out a spray drying process in the usual manner, there is added an ammonium salt of a volatile acid or of an acid which readily decomposes into volatile components, in a concentration of 2—5%, preferably about 3%, and the dried material is brought, during the drying process, to a temperature at which the added salt volatilises.

Surprisingly, with the process according to the present invention, there are obtained dry products which have optimum dissolving properties and, furthermore, are friable to a high degree. Even such extraordinarily hygroscopic medicaments as, for example, sodium chloramphenicol-succinate, are obtained with a dry quality which is not exceeded even by the considerably more expensive freeze drying process. The added materials also have the advantage that they volatilise completely, i.e. they cannot be detected in the final product, even with modern analytical methods, such as gas chromatography. Furthermore, the individual particles of the dry material are, during the drying process, surrounded by a continuously renewed, reducing, ammonia-containing atmosphere which, especially in the case of medicaments which are sensitive to oxidation, forms an additional protection against oxidative decomposition.

The dry substances prepared by the process according to the present invention dissolve again very quickly because of the large surface area due to the characteristic microstructure thereof and, because of the low drying temperatures used, they normally do not contain any decomposition products so that pharmaceuticals thus prepared are especially suitable for parenteral administration.

The process according to the present invention can be carried out continuously in the conventional apparatus used for spray drying without any changes being necessary so that a substantially more economical method of drying is now available, as compared with freeze drying. As drying plant, those have proved to be especially useful which dry the product in co-current and permit a microbe-free separation in a cyclone. The spraying can take place not only with one-substance nozzles but also with two-sub-

stance nozzles, as well as by means of spray plates. The atmospheric humidity is so adjusted according to the evaporation capacity and initial humidity that an air exit temperature of 80°C. is, if possible, not exceeded. In the case of a spray drier with a maximum evaporation capacity of 10 litres of water per hour, there is obtained, with an air throughput of 300 m<sup>3</sup>/hr., an entry temperature of 200°C., the exit temperature thereby being 70—73°C.

Since there is immediately formed a thoroughly dry and friable material, it is prevented from the very beginning that the sprayed wet material remains in the apparatus as a sticky mass or gets into the collecting device still in the form of moist and useless material. For this reason, by means of the process according to the present invention, there can also be prepared readily soluble, friable dried substances from sugar-containing syrups, for example caramel, sweetened condensed milk and malt sugar syrup. Foodstuffs and flavouring materials of low viscosity, such as coffee, cocoa or tea, also give a very readily soluble and friable dried substance which, if desired, can subsequently be granulated.

Since, during the drying procedure, neither inflammable solvent vapours nor aggressive gases are formed, it is possible to omit the provision of additional explosion and corrosion protection for the plant employed.

The following Examples are given for the purpose of illustrating the present invention:—

#### EXAMPLE 1

##### Sodium chloramphenicol-succinate.

By dissolving chloramphenicol-hemisuccinate in water and careful neutralisation with a 10% aqueous solution of sodium hydroxide, there is prepared a 50% aqueous solution of sodium chloramphenicol-succinate. When the neutralisation is completed (pH 6.9), stirring is continued for some time until the yellowish solution has become clear. To this solution is then added a 15% aqueous solution of ammonium bicarbonate in an amount sufficient to give a content of 3% of ammonium bicarbonate, referred to the dry product, and the solution is then subjected to a sterile filtration. Subsequent spray drying of the filtered solution is carried out in a spray drier with a drying capacity of 10 litres of water per hour.

##### Technical data:

amount of air: 300 m<sup>3</sup> per hour  
air entry temperature: 200°C.  
air exit temperature: 70°C.  
throughput: 5 kg. dry substance per hour.

There is obtained a dry product which contains 98.7% sodium chloramphenicol-

succinate and only 1.3% of water; the bulk density is 10 g./30 cc. Since the particle size of the product obtained is only 10–30  $\mu$ m., it dissolves in water extraordinarily quickly and completely.

#### EXAMPLE 2

Chloramphenicol succinate arginine salt. 800 g. chloramphenicol-hemisuccinate are slowly dissolved in 1000 ml. demineralised water, while stirring. Subsequently, 326.3 g. L - (+) - arginine are introduced portionwise. The solution is further stirred for about 45 minutes until clear and, after the addition of 3% ammonium bicarbonate, referred to the solids content, is subjected to a sterile filtration. The filtered solution is spray dried in a spray drier with a capacity of 10 litres of water per hour.

Technical data:  
amount of air: 300 m<sup>3</sup> per hour  
air entry temperature: 190°C.  
air exit temperature: 78°C.  
throughput: 5 kg. dry substance per hour.

The dry product thus obtained contains 98.5% chloramphenicol-succinate arginine salt and 0.9% water, has a bulk density of 10 g./30 cc. and under the microscope gives a characteristic picture of fragmentary or spheroidal particles with a diameter of 10–70  $\mu$ m. This chloramphenicol-succinate arginine salt dissolves completely in 30 seconds in the threefold amount of water at 20°C.

#### EXAMPLE 3

Magnesium chloramphenicol-succinate. 84 g. magnesium hydroxide carbonate are added, with stirring, to 1.4 litres of demineralised water. Into the mixture thus obtained there are subsequently introduced portionwise 735 g. chloramphenicol-hemisuccinate. After stirring for several hours, a clear yellowish solution is obtained which, after the addition of 3% ammonium bicarbonate, referred to the solids content, and after sterile filtration, is spray dried under the conditions described in Example 2.

The dry product thus obtained contains 98.5% magnesium chloramphenicol-succinate and 0.9 water and has a bulk density of 10 g./30 cc.

#### EXAMPLE 4

##### Friable caramel.

11.7 kg. of a 73% caramel solution are diluted with 5.3 kg. water so that there is obtained a 50% solution with a pH value of 4.1. While stirring intensively, 470 g. ammonium bicarbonate are gradually added portionwise, the pH thereby increasing to 7. The solution thus prepared is then spray dried.

Technical data:

entry temperature: 150°C.  
exit temperature: 70°C.  
amount of air: 400 m<sup>3</sup>/hour.

There is obtained a loose and readily friable powder which dissolves spontaneously in water.

#### EXAMPLE 5

##### Friable caramel.

11.7 kg. of a 73% caramel solution are diluted with 5.3 kg. water so that there is obtained a 50% solution with a pH value of 4.1. While stirring intensively, 470 g. ammonium nitrite are gradually added portionwise, the pH thereby increasing to 7. The solution thus prepared is then spray dried.

Technical data:

entry temperature: 150°C.  
exit temperature: 70°C.  
amount of air: 400 m<sup>3</sup>/hour.

There is obtained a loose and readily friable powder which dissolves spontaneously in water.

#### WHAT WE CLAIM IS:—

1. Spray drying process for the preparation of readily water-soluble, friable dry powders or granulates, wherein to the aqueous solution of a substance to be dried, before carrying out the spray drying, there is added an ammonium salt of a volatile acid or of an acid which readily decomposes into volatile components, in a concentration of 2–5% and the material to be dried is brought, during the drying process, to a temperature at which the added salt volatilises.
2. Spray drying process according to claim 1, wherein the ammonium salt is added in a concentration of 3%.
3. Spray drying process according to claims 1 or 2, wherein the ammonium salt used is ammonium bicarbonate or ammonium nitrite.
4. Spray drying process according to any of the preceding claims, whenever used for spray drying a parenterally administrable pharmaceutical.
5. Spray drying process according to claim 4, wherein the parenterally administrable pharmaceutical is a chloramphenicol-succinate salt.
6. Spray drying process according to any of claims 1–3, whenever used for spray drying a solution of a sugar or caramel.
7. Spray drying process according to any of claims 1–3, whenever used for spray drying a liquid foodstuff or flavouring.
8. Spray drying process according to claim 7, wherein the liquid foodstuff or flavouring is milk, coffee, cocoa or tea.
9. Spray drying process according to claim 1 for the preparation of readily water-soluble

and friable dry powders and granulates, substantially as hereinbefore described and exemplified.

- 5 10. Readily water-soluble and friable dry powders, whenever prepared by the process according to any of claims 1—9.

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